Role of the Frank-Starling mechanism during maximal semisupine exercise after oral atenolol

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SUMMARY Reproducible left ventricular dimensions were found by M-mode echocardiography in eight healthy men in the semisupine position during two maximal bicycle exercise tests, performed with four hours interval. Left ventricular end-diastolic dimension did not increase during maximal exercise, while fractional shortening increased by a decrease in end-systolic dimension. Twelve men studied by the same procedure were given 100 mg atenolol orally just after the first test which conspicuously reduced their heart rate response to exercise. End-diastolic dimension increased significantly from rest to peak exercise after the administration of atenolol in contrast to that before beta blockade, and fractional shortening at maximal exercise increased compared with the preceding control test.

We conclude that atenolol changes the left ventricular response to maximal semisupine exercise in normal man, with dilatation and a concomitant increase in systolic myocardial shortening. This suggests that atenolol during maximal exercise reveals the part played by the Frank-Starling mechanism in cardiac reserve. In addition to that mechanism, the increased ventricular emptying is probably also the result of reduced afterload after administration of atenolol.

The Frank-Starling mechanism signifies a direct relation between end-diastolic length and systolic shortening of myocardial fibres. It is operative in isolated heart preparations,^{1,2} left ventricular failure,³ myocardial infarction,⁴ and transplanted hearts.⁵ The role of this mechanism concerning the normal left ventricle, however, remains uncertain.⁶⁻⁸ Cardiac output increases during exercise in normal man⁹ as the result of increases in heart rate⁹ and stroke volume.¹⁰ It is not clear whether the increment in stroke volume is caused by the decrease in end-systolic^{11,12} or the increase in end-diastolic volume (the Frank-Starling mechanism).^{7,8} The conflicting data may be attributed to technical limitations, variations in posture, and varying levels of exercise.

Beta adrenergic receptor blockade reduces the exercise response of heart rate and cardiac output,^{13,14} but does not reduce the stroke volume.^{14,15} This may be compared to the situation in compensated left ventricular failure in which the left ventricle is dilated and stroke volume is maintained. Thus, maintained

stroke volume during exercise after beta blockade may suggest operation of the Frank-Starling mechanism.

The internal dimensions of the left ventricle can be measured non-invasively during exercise by echocardiography.^{16,17} The purpose of this study was firstly to evaluate the role of the Frank-Starling mechanism in normal men during maximal exercise by this method, and secondly to study whether beta adrenergic receptor blockade would increase or unmask such an effect.

Subjects and methods

A group of eight men not given any drug therapy (age range 24 to 38 years, mean 30 years) and a group of 12 men given atenolol (age range 26 to 38 years, mean 33 years) were studied. Four others were excluded because of the unsatisfactory quality of the echocardiograms. All had normal findings by physical examination at rest, including blood pressure, electrocardiogram, and echocardiogram. None had any history of cardiopulmonary disease. All were physically fit but none participated in competitive athletics. Informed consent was obtained from all subjects before the study.

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BICYCLE EXERCISE

Graded exercise was performed on an electrically braked bicycle ergometer in the semisupine position with a 20° head-up tilt. The initial work load was 50 W for three minutes with subsequent increase by 50 W every three minutes until exhaustion. All subjects performed two exercise tests with an interval of four hours. The highest achieved work load common to both tests was defined as the maximal exercise level for each subject.

BETA ADRENERGIC BLOCKADE

The subjects given atenolol received a single dose, 100 mg orally, within five minutes after the first exercise test. The second exercise test was performed four hours after drug intake, since peak plasma levels occur two to four hours after oral administration.¹⁸

ECHOCARDIOGRAPHY

M-mode echocardiograms were obtained using an SKI Ekoline 20A Echocardiograph interfaced with a Honeywell strip-chart recorder at paper speed 100 mm/s, with a hand-held 2.25 MHz transducer in the standard intercostal space¹⁹ at the left sternal border. Heart rate was measured from simultaneously recorded electrocardiograms. Measurements were made at the level of the chordae tendineae between

the leading edges of echoes from the left border of the interventricular septum and from the posterior wall endocardium. Left ventricular end-diastolic dimension was measured at the onset of the QRS complex and end-systolic dimension on the vertical axis at the peak anterior excursion of the posterior wall (Fig. 1). The measurements were made during expiration and represented the average of at least three heart cycles. Fractional shortening was calculated as $(\text{EDD} - \text{ESD}) / \text{EDD} \times 100\%$ where EDD=end-diastolic dimension and ESD=end-systolic dimension. Recordings were made at rest with the feet on the ergometer pedals, during the last 30 seconds of each exercise level, and at one, three, five, and 10 minutes after termination of exercise, with the feet still on the pedals.

STATISTICAL ANALYSIS

Wilcoxon's two-tailed test for comparison of paired data was used.²⁰ Differences were considered significant when $p < 0.05$.

Results

NO DRUG INTERVENTION

The duration of exercise was 14.1 ± 2.0 (mean $\pm$ SD) minutes in the first and 13.8 ± 2.1 minutes in the sec-

Fig. 1 Echocardiograms from one subject (A) at rest with heart rate 62 beats/min showing measurements of left ventricular end-diastolic (EDD) and end-systolic dimension (ESD), and (B) during the 13th minute of semisupine bicycle exercise with heart rate 174 beats/min.

Table 1 Cardiac response to maximal semisupine exercise without drug intervention (n=8)

	Heart rate (beats/min)	EDD (mm)	ESD (mm)	FS (%)
First test				
Rest	69±8	50.5±2.7	32.9±2.7	34.9±3.8
Exercise	176±12	49.5±3.1	26.3±5.0	47.8±7.8
p	<0.01	<0.05	<0.01	<0.01
Second test				
Rest	69±6	49.1±3.2	33.1±2.8	32.6±4.0
Exercise	179±9	48.9±2.6	26.9±3.4	44.9±6.4
p	<0.01	NS	<0.05	<0.05

Values are mean ±SD. Abbreviations: EDD, end-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening.

ond test (NS), while the maximal work loads were 256±32 W and 250±38 W, respectively (NS).

Heart rate, left ventricular dimensions, and fractional shortening at rest and maximal exercise in both exercise tests are shown in Table 1. A small reduction in end-diastolic dimension was seen during exercise in the first test (p<0.05) but not in the second test (Table 1). Fractional shortening conspicuously increased in both exercise tests because of a decrease in end-systolic dimension.

Except for a minor difference at six minutes of exercise there were no significant differences in heart rate between the two tests (Fig. 2). There was a 1.4±0.9 mm decrease in end-diastolic dimension at

rest from the first to the second test (p<0.05), but the reduction did not exceed 2 mm in any of the subjects. End-diastolic dimension did not differ significantly between the two tests at any exercise level or in the recovery period (Fig. 3). No significant differences between the two tests were found concerning end-systolic dimension (Fig. 3) or fractional shortening (Fig. 4).

BETA ADRENERGIC BLOCKADE

The duration of exercise decreased from 13.8±2.2 minutes before to 12.5±2.0 minutes after atenolol administration (p=0.01), and the maximal work loads were 246±33 W and 229±33 W, respectively (NS).

Heart rate, left ventricular dimensions, and fractional shortening at rest and maximal exercise before and after administration of atenolol are shown in Table 2.

The heart rate was lowered by atenolol at rest, and throughout the exercise and recovery period (Fig. 5). The most pronounced reduction in heart rate was

Fig. 2 Heart rate in eight normal men during maximal bicycle exercise in semisupine position performed with four hours interval. Closed circles = first test. Open circles = second test. Values are mean ±SD.

Fig. 3 Left ventricular end-diastolic (EDD) and end-systolic dimension (ESD) in eight normal men during maximal bicycle exercise in semisupine position performed with four hours interval. Symbols and expression of values as in Fig. 2.

Table 2 Effects of atenolol on cardiac response to maximal semisupine exercise (n=12)

	Heart rate (beats/min)	EDD (mm)	ESD (mm)	FS (%)
Control				
Rest	66±10	50.3±2.6	33.1±2.5	34.7±4.2
Exercise	161±13	51.3±2.9	28.2±3.5	44.9±6.9
p	<0.001	NS	<0.01	<0.01
Atenolol				
Rest	52±6	49.1±2.7	33.4±2.4	31.9±3.5
Exercise	120±9	53.6±3.2	25.6±2.7	52.3±4.5
p	<0.001	<0.001	<0.001	<0.001

Values are mean ±SD. Abbreviations as in Table 1.

Fig. 4 Fractional shortening in eight normal men during maximal bicycle exercise in semisupine position performed with four hours interval. Symbols and expression of values as in Fig. 2.

Fig. 6 Left ventricular end-diastolic (EDD) and end-systolic dimension (ESD) in 12 normal men during maximal bicycle exercise in semisupine position performed just before and four hours after 100 mg atenolol orally. Symbols and expression of values as in Fig. 5.

Fig. 5 Heart rate in 12 normal men during maximal bicycle exercise in semisupine position performed just before (closed triangles) and four hours after 100 mg atenolol orally (open triangles). Values are mean ±SD.

Fig. 7 Fractional shortening in 12 normal men during maximal exercise in semisupine position performed just before and four hours after 100 mg atenolol orally. Symbols and expression of values as in Fig. 5.

found at the highest exercise level.

End-diastolic dimension increased significantly from rest to maximal exercise after administration of atenolol in contrast to that before atenolol (Table 2), and was then significantly higher than in the control test at peak exercise and immediately afterwards (Fig. 6). End-systolic dimension was reduced by atenolol only at the maximal exercise level (Fig. 6).

After administration of atenolol, fractional shortening decreased at rest and the lowest exercise levels while it increased at maximal exercise (Fig. 7). The pre-exercise relation with lower fractional shortening after beta blockade was re-established after 10 minutes of recovery.

Discussion

Echocardiography is an accurate and reproducible method for assessment of left ventricular dimensions at rest,^{19 21} and, as recently shown, also during exercise.¹⁶ In this study we could show reproducible echocardiographic data when two maximal exercise tests in the semisupine position were performed with an interval of four hours. A small but significant difference in end-diastolic dimension at rest was found between the two tests, but not during exercise or recovery. The difference in end-diastolic dimension, however, was only 1.4 mm and was well within the limits of variation of the method,^{19 22} and we therefore do not regard this as representing a real change in left ventricular dimension.

The subjects cycled to exhaustion. Though oxygen uptake was not measured, the exercise level achieved must be regarded as near maximal when considering the heart rate response.²³ The experimental design of this study thus allowed comparison of left ventricular dimensions during maximal exercise before and after drug intervention.

Our finding of reduced end-systolic dimension from rest to maximal exercise without simultaneously increased end-diastolic dimension indicates increased stroke volume by augmentation of left ventricular emptying without left ventricular dilatation. This is in accordance with other echocardiographic investigations,^{16 17 24} though lower exercise levels were used in these studies. It is also in agreement with the slight increment in mean pulmonary wedge pressure found in normal men during maximal supine exercise,²⁵ reflecting a very modest increase in preload. Conflicting results were recently reported, however, in an echocardiographic study where end-diastolic dimension increased during semisupine cycling, with a simultaneous increase in fractional shortening primarily caused by the change in end-diastolic dimension.⁷ The lack of a significant decrease in end-systolic dimension at any exercise level compared with rest in

that study is in contrast to our findings and those of others.^{16 17 24} Increase in end-diastolic dimension during exercise has been found in dogs.^{26 27} These studies are, however, probably not directly comparable with the present study since the dogs performed exercise in the standing position while the semisupine position was used in our study.

Atenolol induced an increase in end-diastolic dimension during maximal exercise, indicating dilatation of the left ventricle. The higher fractional shortening at maximal exercise during beta blockade than in the control test probably reflects an increase in systolic myocardial shortening. Our finding of left ventricular dilatation during exercise after beta blockade is in agreement with the distinct increase in left ventricular filling pressure observed in normal men after intravenous administration of propranolol.^{14 25} The dilatation cannot be explained by increased afterload since systolic blood pressure during exercise is lower after beta blockade than before.^{13 28 29} The decrease in fractional shortening after atenolol at low exercise levels is similar to that found after propranolol in normal subjects who performed mild bicycle exercise in a supine position.³⁰ At higher exercise levels, we found no indication of a decrease in stroke volume since fractional shortening did not change at moderate exercise and even increased at maximal exercise. Recent radionuclide angiographic studies showed no change in stroke volume during severe exertion after propranolol.^{15 25} The stroke index during heavy exercise even increased after long term treatment with atenolol in patients with low grade hypertension.³¹

Our findings indicate increased left ventricular diastolic filling after beta blockade at peak exercise, with a simultaneous increase in systolic myocardial shortening. This suggests that during maximal exercise atenolol shows the part played by the Frank-Starling mechanism in cardiac reserve. Left ventricular performance has been found to be dependent also on changes in afterload, as shown by reduced echocardiographic indices of myocardial shortening in normal human subjects after an acute increase in systolic blood pressure.³² Thus, the increase in fractional shortening at peak exercise after beta blockade in the present study may also be explained by the easier ventricular emptying caused by decreased afterload, since systolic blood pressure during exercise is reduced by atenolol.^{28 29} Systemic vascular resistance in patients with coronary artery disease has been found to increase during rest after the intravenous administration of both propranolol¹⁴ and atenolol.³³ During exercise, however, systemic vascular resistance increased after propranolol¹⁴ but did not change significantly after atenolol,³³ probably reflecting the difference in cardioselectivity between the two beta blockers. It may be speculated that the difference in

effect on peripheral resistance during exertion, supposing it is present also in normal subjects, may explain why fractional shortening increased after atenolol during peak exercise in our study in contrast to the reduced ejection fraction during heavy exercise reported after propranolol.^{15 25} The increase in fractional shortening might suggest incomplete beta blockade. This is, however, unlikely considering the demonstrated reduction in heart rate at maximal exercise, and since little difference has been found between the effects of 100 and 200 mg atenolol on heart rate during exertion.³⁴

The evidence of the Frank-Starling mechanism during exercise after atenolol when the reduction in heart rate became most obvious may be compared to the left ventricular response to exercise in recipients of cardiac transplants. The Frank-Starling mechanism has been shown to be operative in these patients early in exercise when chronotropic and inotropic influences were low because of denervation of the heart.⁵ It was, however, not operative later in exercise when levels of circulating catecholamines rose and cardiac output increased by means of tachycardia.

Our findings thus indicate that atenolol discloses the part played by the Frank-Starling mechanism in cardiac reserve with left ventricular dilatation and increased systolic myocardial shortening during maximal semisupine exercise in normal men. The increased ventricular emptying is probably also the result of a reduction in afterload after administration of atenolol.

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